The use of antibiotic therapy as an adjunct in treatment of bone and joint infections

IN OTHERWISE HEALTHY CHILDREN, ACUTE BONE AND JOINT infections can be managed effectively using a sequential intravenous-oral antibiotic regimen (1-12). This approach offers several advantages over the traditional alternative of three to six weeks of in-hospital intravenous therapy, including: decreased risk of complications associated with intravenous lines; greater comfort and ease of therapy for the patient; decreased cost; and, for the child who is able to complete oral therapy at home, a shorter stay in hospital. Therapeutic failure with development of chronic infection is a theoretical but rare occurrence that should be avoidable provided patients are carefully selected and monitored. The Canadian Paediatric Society has reviewed the available data in order to outline the clinical situations in which a sequential intravenous-oral antibiotic regimen should be considered as well as to emphasize the important principles of management that must be employed if such therapy is to be successful.

WHEN SHOULD SEQUENTIAL INTRAVENOUS-ORAL ANTIBIOTIC THERAPY BE CONSIDERED?

The following conditions are most conducive to successful outcome of oral therapy:

- Normal, immunocompetent host before infection;
- Acute hematogenous osteomyelitis or septic arthritis;
- Seven days or less duration of signs and symptoms before therapy;
- Older than three months of age;
- Absence of any condition that might hamper antibiotic ingestion and absorption;
- Infection caused by *Haemophilus influenzae* type b, *Staphylococcus aureus*, *Streptococcus pneumoniae* or group A beta hemolytic streptococcus;
- Bacterial isolate recovered and saved from

culture of blood and/or bone/joint aspirate(s). (NOTE: if blood is the only source of culture, an etiological agent is recovered in 30 to 60% of cases versus 85% when bone and/or joint aspirates are also obtained for culture [13,14]);

- Demonstration that the bacterial isolate is susceptible to an appropriate orally administered antibiotic;
- Capability for laboratory monitoring of blood antibacterial activity.

These conditions are satisfied in the majority of cases of acute bone or joint infections in children. In their absence, oral therapy still may be possible, but only after careful consideration of the specifics of each case.

WHEN CAN ORAL THERAPY BE STARTED?

Once there is evidence of definite clinical improvement in both systemic and local signs of inflammation and the child is eating normally, oral therapy can be considered. This status usually occurs within several days of hospitalization, although convalescence may be slower in children with more extensive disease or in whom surgical intervention was necessary. Special consideration is required for children one year of age or younger, since they have the highest incidence of complications following bone and joint infections, especially those involving the hip. A decline in erythrocyte sedimentation rate (ESR) may lag behind other evidence of disease resolution, and thus is not a reliable guide for deciding when to start oral therapy (1,13,14).

WHAT ANTIBIOTICS ARE APPROPRIATE FOR USE IN ORAL THERAPY?

The dosage of oral antibiotic is two- to threefold higher than what would normally be used for treating less serious out-patient infections. Surprisingly, gastrointestinal intolerance with such high doses is uncommon (1).

The majority of bone and joint infections in children are caused by *S aureus* or *H influenzae*. The choices and dosage regimens for oral antibiotics to treat these isolates are indicated in Table 1. Group A beta hemolytic

Correspondence and reprints: Infectious Diseases and Immunization Committee, Canadian Paediatric Society, 401 Smyth Road, Ottawa, Ontario K1H 8L1. Telephone (613) 737-2728, Fax (613) 737-2794

TABLE 1

Choice of oral antibiotics for completing therapy of acute hematogenous bone or joint infections in children

Specific etiology	Antibiotic	Daily dose
<i>Staphylococcus aureus</i>		
penicillin-sensitive	Penicillin V	100 mg/kg divided every 6 h
penicillin-resistant	Cloxacillin	150 to 200 mg/kg divided every 6 h
	Flucloxacillin	100 mg/kg divided every 6 h
	Cephalexin	100 mg/kg divided every 6 h
	Clindamycin	30 mg/kg divided every 6 to 8 h
<i>Haemophilus influenzae</i>		
ampicillin-sensitive	Amoxicillin	100 mg/kg divided every 6 to 8 h
	Pivampicillin	100 mg/kg divided every 6 to 12 h
ampicillin-resistant	Cefixime	8 mg/kg divided every 24 h
	Chloramphenicol	75 mg/kg divided every 8 h

*Alternate regimens are possible and expert advice should be sought. Use of chloramphenicol requires monitoring of complete blood cell count as well as serum antibiotic concentration. Note: for *S pneumoniae* or group A beta hemolytic streptococcus, penicillin V, amoxicillin, pivampicillin, cephalexin or clindamycin can be used, in doses as shown

streptococcus and *S pneumoniae* can be treated with penicillin V, amoxicillin, pivampicillin or cephalexin using similar doses to those shown in the table. Regarding choices for staphylococcal infections, cloxacillin suspension has an exceptionally bad taste that may decrease compliance. Flucloxacillin is a slightly more palatable alternative that also provides approximately twice the serum concentration as that achieved with an equivalent dose of oral cloxacillin (4,5). Cephalexin suspension is the most palatable alternative and is well tolerated in large doses. For children allergic to penicillins and cephalosporins, alternate drugs include clindamycin and chloramphenicol, as shown in the table.

WHAT ARE THE INDICATORS OF SUCCESSFUL TREATMENT?

Clinical and laboratory evidence of resolution of infection and associated inflammation should be meticulously documented in all children with bone and joint infections irrespective of the route of therapy. There should be resolution of fever, progressive decrease in local signs of inflammation and resumption of normal skeletal function. Although ESR often increases during the first week of hospitalization, subsequent gradual return to normal is an excellent predictor of successful outcome and may be used to determine the end-point of therapy.

HOW SHOULD ORAL THERAPY BE MONITORED?

The key strategy for monitoring oral antibiotic therapy of bone and joint infections is demonstration that drug absorption is adequate to achieve therapeutic serum concentrations. Despite the high doses used, up to 10% of children receiving oral penicillins and cephalosporins will have less than adequate absorption (1). Thus, oral therapy should not be undertaken unless the serum level of antibiotic can be monitored in some way.

A relatively simple way to assess the adequacy of antibiotic absorption is to determine the serum bacte-

riocidal titre (SBT) for orally administered penicillins and cephalosporin, or the serum inhibitory titre (SIT) for oral clindamycin. For both the SIT and SBT, the original bacterial isolate is added to serial dilutions of the patient's serum sampled at a time of expected peak antibiotic concentration (45 to 90 mins after an oral dose). The initiation of oral therapy needs to be coordinated with the laboratory so that an SIT/SBT can be done approximately 24 h after starting oral therapy. The test takes 24 h (SIT) to 48 h (SBT) to complete. If there is concern about inadequate drug absorption, intravenous therapy can be resumed while awaiting results. The laboratory records the highest dilution of serum in which 99.9% or more of the patient's original bacterial inoculum has been inhibited (SIT) or killed (SBT). The desired peak titre is $\geq 1:8$.

Failure to achieve this level may be due to: an insufficient dose of antibiotic (due to medication error, lack of compliance, or emesis); inappropriate timing of obtaining the post-dose blood sample; delay in getting the sample to the laboratory; or laboratory error. If any of these occurs, the test should be repeated. Alternately, gastrointestinal absorption of antibiotic may have been inadequate, in which case consideration must be given to an alternate oral antibiotic regimen or returning to treatment with intravenous antibiotics. In general, the SIT/SBT should be repeated each time there is a change in the type or dose of antibiotic.

WHEN IS OUT-PATIENT TREATMENT WITH ORAL THERAPY APPROPRIATE?

Compliance is the key factor to be considered in deciding whether a child should be allowed to complete the therapeutic course at home. Unless a physician is totally confident that the child's guardians will ensure that all doses of the drug are given as prescribed, completion of oral therapy should be carried out in hospital. If it is decided that the child can be discharged home, it is essential that there be weekly supervision for the remainder of the treatment course, in order to

monitor the child's clinical status and compliance with medication. This can be done through a combination of clinic visits and telephone contacts. If there are doubts about compliance, a repeat SIT/ST should be done.

HOW LONG SHOULD THERAPY BE CONTINUED?

Whether therapy is given entirely by intravenous or sequential intravenous-oral routes, the minimal duration of therapy is: for septic arthritis, two weeks if caused by *H influenzae* and three weeks if caused by *S aureus*, *S pneumoniae*, or group A beta hemolytic streptococcus; for osteomyelitis, four weeks. Therapy should be extended if there is still clinical or laboratory evidence of inflammation.

CONCLUSION

This summary is not meant to be an exhaustive review. The outcome of treatment of skeletal infection is a function of numerous variables, including the characteristics of both the pathogen and the host, the site of involvement, the duration of disease before treatment, the adequacy of surgical intervention and the provision of effective antibiotic therapy. When possible, multidisciplinary management of children with bone and/or joint infection is optimal and should include individuals with expertise in pediatrics for overall patient care and coordination of subspecialty input; orthopedic surgeons for advice and assistance about the use of surgical intervention for etiological diagnosis and management; and infectious disease specialists for advice, and assistance about appropriate specimen collection and handling for bacterial culture, as well as subsequent initiation and monitoring of oral antibiotic therapy.

REFERENCES

1. Nelson JD, Bucholz RW, Kusmiesz H, Shelton S. Benefits and risks of sequential parenteral-oral cephalosporin therapy for suppurative bone and joint infections. *J Pediatr Orthop* 1982;2:255-62.
2. Prober CG. Oral antibiotic therapy for bone and joint infections. *Pediatr Infect Dis* 1982;1:8-10.
3. McCracken GH Jr. New era for orally administered antibiotics: Use of sequential parenteral-oral antibiotic therapy for serious infectious diseases of infants and children. *Pediatr Infect Dis J* 1987;6:951-3.
4. Nelson JD, Howard JB, Shelton S. Oral antibiotic therapy for skeletal infections of children. *J Pediatr* 1978;92:131-4.
5. Tetzlaff TR, Howard JB, McCracken GH Jr, Calderon E, Larrondo J. Antibiotic concentrations in pus and bone of

- children with osteomyelitis. *J Pediatr* 1978;92:135-40.
6. Green JH. Cloxacillin in treatment of acute osteomyelitis. *Br Med J* 1967;2:414-6.
7. Feigin RD, Pickering LK, Anderson D, Keeney RE, Shackelford PG. Clindamycin treatment of osteomyelitis and septic arthritis in children. *Pediatrics* 1975;55:213-23.
8. Rodriguez W, Ross S, McKay D, Moskowitz P. Clindamycin in the treatment of osteomyelitis in children. A report of 29 cases. *Am J Dis Child* 1977;131:1088-93.
9. Tetzlaff TR, McCracken GH Jr, Nelson JD. Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis. *J Pediatr* 1978;92:485-90.
10. Prober CG, Yeager AS. Use of the serum bactericidal titer to assess the adequacy of oral antibiotic therapy in the treatment of acute hematogenous osteomyelitis. *J Pediatr* 1979;95:131-5.
11. Kolyvas E, Ahronheim G, Marks MI, Gledhill R, Owen H, Rosenthal L. Oral antibiotic therapy of skeletal infections in children. *Pediatrics* 1980;65:867-71.
12. Kaplan SL, Mason EO Jr, Feigin RD. Clindamycin versus nafcillin or methicillin in the treatment of *Staphylococcus aureus* osteomyelitis in children. *South Med J* 1982;75:138-42.
13. Dich VQ, Nelson JD, Haltalin KC. Osteomyelitis in infants and children. *Am J Dis Child* 1975;129:1273-8.
14. Welton CJ, Long SS, Fisher MC, Alburger PD. Pyogenic arthritis in infants and children: A review of 95 cases. *Pediatr Infect Dis J* 1986;5:669-76.

Canadian Paediatric Society, Infectious Diseases and Immunization Committee

Members: Donald Clogg (director responsible), Alberta Children's Hospital, Calgary, Alberta; Noni E MacDonald (chair), Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Gilles Delage, Adjoint médical, Service de transfusion de sang de la Croix-Rouge canadienne, Centre de Montréal, Montréal, Québec; Scott Halperin, Department of Pediatrics, IWK Children's Hospital, Halifax, Nova Scotia; Taj Jadavji, Department of Pediatrics, Alberta Children's Hospital, Calgary, Alberta; Susan King, Division of Infectious Disease, Hospital for Sick Children, Toronto, Ontario; Barbara Law (principal author), Pediatric Infectious Diseases, University of Manitoba, Winnipeg, Manitoba; Marc Lebel, Département de pédiatrie, Hôpital Sainte-Justine, Montréal, Québec. **Consultants:** Ronald Gold, Division of Infectious Disease, Hospital for Sick Children, Toronto, Ontario; Victor Marchessault, Children's Hospital of Eastern Ontario. **Liaisons:** Public Health, Dr Jacqueline Carlson, Disease Control and Epidemiology; Public Health Branch, Toronto, Ontario; Comité d'immunisation du Québec, Dr Pierre Déry, Centre hospitalier de l'Université Laval, Ste-Foy, Québec; American Academy of Pediatrics, Dr Dan Granoff, Washington University, School of Medicine, St Louis, Missouri; Centre for Vaccine Evaluation, Dr David Scheifele, Division of Infectious Diseases, Research Centre, BC's Children's Hospital, Vancouver, British Columbia; **Epidemiology:** Dr John Waters, Alberta Health, Communicable Disease Control, Edmonton, Alberta